

The University of Chicago

THE PREPARATION OF THREO- α , β
DIHYDROXY-BUTYRALDEHYDE

A DISSERTATION SUBMITTED TO THE FACULTY OF THE
DIVISION OF THE PHYSICAL SCIENCES IN CANDIDACY
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY
1938

By
DAVID CHANTRILL SPAULDING

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THE PREPARATION OF THREE- α,β DIHYDROXY-BUTYRALDEHYDE

INTRODUCTION

For a number of years, these laboratories have been interested in the problem of the mechanism of sugar oxidation in alkaline solution. The results of numerous researches on this subject have been reported by Nef and his students. During the course of this work the formation of saccharinic acids in the reaction mixtures was demonstrated. The saccharinic acids are rearrangement products and not oxidation products of the sugars. They are formed by the action of alkalis on the sugars and are therefore possible products in any reaction mixture obtained from sugars in alkaline solution. Because of these facts it was determined some years ago to attempt to throw some light on the conditions necessary for, the extent of, and the mechanism of saccharinic acid formation from sugars in order to determine how important a factor this rearrangement is in the alkaline oxidation experiments with sugars.

As very little was known about the properties of individual saccharinic acids, it was necessary first of all to prepare and study some of them. The group of C_4 -saccharinic acids was chosen for this study because there are only eleven of these that are theoretically possible as saccharinic acid rearrangement products of the tetroses, and it seemed possible to prepare and study all of these. This has now been accomplished, the preparation of the last member of the group having been recently reported by Glattfeld and Schneider.¹ The properties of the individual C_4 saccharinic acids are now fairly well known.

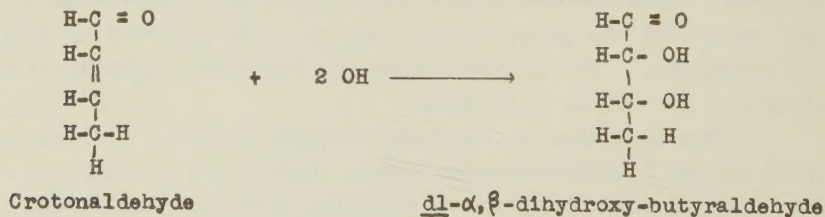
The next step in the broad program laid out was the preparation of the four-carbon-atom aldose sugars as a preliminary to the study of their behavior in alkaline solution. While the literature on the preparation of the aldo-tetroses, erythrose and threose, is rather extensive, there is as yet no good method for their preparation in the pure state and in good yields. They can be best obtained by degradation of the aldo-pentoses. Degradative processes

¹Glattfeld, and Schneider, J. Am. Chem. Soc., **60**, 415 (1938).

are notoriously unsatisfactory as methods of synthesis and the degradation of sugars is no exception. Other means of preparation were therefore sought. A rather promising method seems to have been found in the reduction of the acetylated acid chlorides of dl-erythronic and dl-threonic acids. Methods of preparation of these acids have been devised in these laboratories and some success already attained in the reduction of the acetylated acid chloride of dl-erythronic acid.²

The aldo-tetroses were chosen for the saccharinic acid rearrangement study because of the small number of C₄-saccharinic acids that are theoretically possible as rearrangement products of these sugars. This small number makes the chances of successful isolation from mixtures containing them very good. As soon as some success had been attained in the reduction of acetylated dl-erythronic acid chloride, it was realized that it might be possible to reduce the C₄-saccharinic acids in the same way and thus obtain hydroxy aldehydes very closely related to the tetroses but of still simpler structure. These aldehydes, under the influence of alkalis, would give a still smaller number of rearrangement products and would therefore be even better than the tetroses for the study of the rearrangement mechanism. Two of the C₄-saccharinic acids have been so far successfully reduced in this laboratory.^{3,4}

Other methods of synthesis for the aldehydes corresponding to the C₄-saccharinic acids have been sought. Crotonaldehyde is a commercial product at present and is a possible source for dl- α,β -dihydroxy-butyraldehyde as the following equation indicates:



The problem assigned to me was the study of the reaction

²Bertram D. Kribben, Ph.D. dissertation, Department of Chemistry, University of Chicago (1938).

³Glattfeld and Mochel, *J. Am. Chem. Soc.*, **60**, 1011 (1938).

⁴Glattfeld and Straitiff, *ibid.*, 1384 (1938).

illustrated by the equation above, with a view to discovering a procedure for the preparation of the dihydroxy-aldehyde in good yield.

THE LITERATURE

But four papers could be found in the literature dealing with the methyl-trioses, of which group the above dl- α,β -dihydroxy-butyraldehyde is a member. The first of these is by Wohl and Frank,⁵ who converted crotonaldehyde into dl- α,β dihydroxy-butyraldehyde, which they called methylglycerinaldehyde, by a series of steps in which the substances of the following formulas were successively used:

- | | |
|--|-------------------------------|
| (1) $\text{CH}_3\cdot\text{CH}=\text{CH}\cdot\text{CHO}$ | Crotonaldehyde |
| (2) $\text{CH}_3\cdot\text{CHCl}\cdot\text{CH}_2\cdot\text{CH}(\text{OC}_2\text{H}_5)_2$ | Chlorobutyralacetal |
| (3) $\text{CH}_3\cdot\text{CH}:\text{CH}\cdot\text{CH}(\text{OC}_2\text{H}_5)_2$ | Crotonacetal |
| (4) $\text{CH}_3\cdot\text{CHOH}\cdot\text{CHOH}\cdot\text{CH}(\text{OC}_2\text{H}_5)_2$ | Methylglycerinaldehyde acetal |
| (5) $\text{CH}_3\cdot\text{CHOH}\cdot\text{CHOH}\cdot\text{CHO}$ | Methylglycerinaldehyde |

The methylglycerinaldehyde obtained was a colorless syrup which contained 21 per cent of water. When the water was completely removed from a small sample by drying to constant weight over phosphorus pentoxide, the sample gave a good analysis for carbon and hydrogen. Further evidence that the syrup contained methylglycerinaldehyde was found in the facts that it gave a phenylosazone and a benzyl-phenyl-hydrazone of proper analysis. The former melted at $171.5^\circ(\text{corr.})$ and the latter at 116°C .

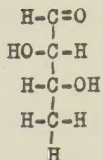
Wohl and Frank did not attempt to classify their compound as having a cis or a trans configuration, or in the newer nomenclature, as being of the "erythro" or "threo" form. From the fact that crotonaldehyde exists as the trans isomer,⁶ and the fact that they used potassium permanganate as an oxidizing agent, which causes a "cis addition" of hydroxyl groups to unsaturated compounds,⁷ it is probable that they obtained the threo form of the aldehyde,

⁵Wohl, and Frank, Ber. 35, 1904-08 (1902).

⁶Blacet, Young, and Roof, J. Am. Chem. Soc., 59, 608-14 (1937).

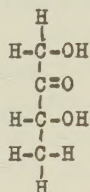
⁷Geza Braun, ibid., 51, 237 (1929).

namely:



This conclusion receives support from the facts reported in this paper.

The second paper is by Dills and Stephan.⁸ These authors report the preparation of a ketose of the structure:



Their synthesis of this compound involved successive preparations of substances of the following formulas:

- | | |
|--|-----------------------------|
| (1) $\text{CH}_3 \cdot \text{CO} \cdot \text{CHOH} \cdot \text{CH}_3$ | Dimethyl ketol |
| (2) $\text{CH}_3 \cdot \text{CO} \cdot \text{CHOCOC}_6\text{H}_5 \cdot \text{CH}_3$ | Benzoyl dimethyl ketol |
| (3) $\text{CH}_2\text{Br} \cdot \text{CO} \cdot \text{CHOCOC}_6\text{H}_5 \cdot \text{CH}_3$ | Bromobenzoyl dimethyl ketol |
| (4) $\text{CH}_2\text{OH} \cdot \text{CO} \cdot \text{CHOH} \cdot \text{CH}_3$ | Hydroxy dimethyl ketol |

The product is a methyl keto-triose and is reported to have the properties to be expected from a compound of this structure. It was obtained as a yellow syrup which gave a phenylosazone of the same melting point as that of Wohl and Frank. It gave a proper carbon and hydrogen analysis and there seems to be little doubt as to its identity.

Recently, Glattfeld and Mochel⁹ prepared dl-1,2 dihydroxy-isobutyraldehyde by the reduction of the acid chloride of dl-1,2 diacetoxy-isobutyric acid according to the procedure developed by Cook and Major¹⁰ for the reduction of acid chlorides, followed by deacetylation, while Glattfeld and Straitiff reported the prepara-

⁸Dills, and Stephan, Ber. 42, 1787 (1909).

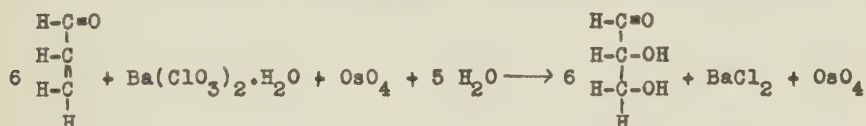
⁹Glattfeld, and Mochel, loc. cit.

¹⁰Cook, and Major, J. Am. Chem. Soc., 58, 2410 (1936).

tion of dl-erythro α , β dihydroxy-butylaldehyde from the corresponding acid by the use of the same method.¹¹

EXPERIMENTAL PART

As mentioned above, it is probable that Wohl and Frank had prepared dl-threo α , β dihydroxy-butylaldehyde, but, because of the number of steps involved in their procedure, and the consequent low overall yield, it was decided to try to use a method of oxidation that I. S. Neuberg¹² had found successful in the preparation of dl-glyceraldehyde from acrolein. She found that the acrolein could be oxidized directly to glyceraldehyde by the use of barium chlorate activated by osmium tetroxide, according to the equation:



She carried out the reaction in the following manner. Thirty-seven grams (0.67 mole) of freshly-distilled acrolein and 112 grams (0.35 mole) of crystalline barium chlorate [$\text{Ba}(\text{ClO}_3)_2 \cdot \text{H}_2\text{O}$] were dissolved in 320 cc. of water. To this solution was added 0.2 gram of osmium tetroxide dissolved in about 100 cc. of water. The mixture was thoroughly shaken and then cooled to -8°C ., at which temperature it was kept for twelve hours. It was then allowed to warm up to 0°C ., kept at this temperature for four days, and then allowed to stand at room temperature for two days. At the end of this period, all of the acrolein had disappeared. The solution was exactly neutralized with a solution of barium hydroxide, and then concentrated to a thick syrup at reduced pressure. The residue was repeatedly extracted with absolute alcohol, the alcohol removed from the extract by distillation at reduced pressure, and the triose obtained as a thick syrup in a yield of 64 per cent. Seeding the syrup with pure crystalline glyceraldehyde brought about the crystallization of a part of the syrup, so that Neuberg was able to report an overall yield of 22 per cent of the crystalline product, which melted at $132-138^\circ\text{C}$.

It was proposed to apply this procedure to the problem of

¹¹Glattfeld, and Straitiff, loc. cit.

¹²I.S. Neuberg, Biochem. Zeit., **255**, 1-26 (1932).

the oxidation of crotonaldehyde to α , β -dihydroxy-butyraldehyde. The first experiment carried out showed that an acidic product was formed together with the desired aldehyde and it was at once suspected that this production of acid reduced the yield of the aldehyde. Neuberg reported the formation of an acidic product in the oxidation of acrolein, but did not identify it. It was decided, therefore, to run a number of small-scale oxidation experiments in which the various factors involved in the reaction were successively varied, so as to determine the conditions by which the acid formation might be kept at a minimum. The course of the reaction in these experiments was followed as indicated below.

The total extent of the oxidation reaction was determined by a Volhard analysis for chloride ion (formed by the reduction of the chlorate). In later experiments, in which silver chlorate was used in place of the barium salt, this was done by analysis for silver ion by titration with thiocyanate. Thus, a simple subtraction of the concentration of silver ion present at any given time from the amount of silver ion initially present, or the increase in chloride ion concentration when barium chlorate was used, gave a measure of the extent of the oxidation.

The formation of acidic constituents was followed by titration with standard alkali to the phenolphthalein end-point. From the titration figures, and on the assumption that the acid was formed entirely from the aldehyde, it was possible to compare the efficiency of various procedures as to the yield of the sugar.

On the assumption that the dihydroxy-aldehyde was the only constituent of the solution that reduced Benedict's solution,¹³ the extent of its formation could be followed by simple titrations of aliquot portions of the reaction solution with that reagent at various times. Wohl and Frank reported that their syrup possessed but 60 per cent of the reducing power of d-glucose and this figure

¹³Pure crotonaldehyde will reduce Benedict's solution, although incompletely, a green colored solution being formed in contrast to the usual colorless solution. The effect of the crotonaldehyde present in the reaction mixtures was disregarded in these tests since an experiment showed that the addition of one gram of crotonaldehyde to a solution of one gram of the sugar syrup in 50 cc. of water (approximately the concentration of the reaction mixture when the reaction had gone one-half to completion) did not affect the reducing power of the original solution. This is explained by the greater reducing power of the syrup compared to that of the crotonaldehyde.

was used as the basis for quantitative calculations in these preliminary tests.

Some attempts were also made to follow the disappearance of the crotonaldehyde from the reaction mixture by means of iodine or bromine absorption. However, they were abandoned when it was found that these reagents attack the sugar very readily, oxidizing it to α,β -dihydroxy-butyric acid.

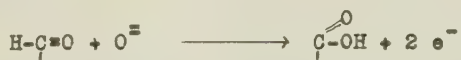
Altogether, sixteen separate small-scale oxidation experiments were made in addition to six duplicates which provided checks on the reproducibility of results in the methods of analysis. The results are recorded in Table 1. The factors studied were: a) the effect of temperature (1-3); b) the effect of concentration (4-7); c) the effect of the amount of osmic acid present per mole of crotonaldehyde (8-12); d) the effect of the acidity of the solution (13-15); and e) the effect of the change in the type of chlorate used (16).

As stated above, it is possible to determine the total number of equivalents of oxidizing power that have been used up as well as the number of equivalents of acid that have been formed during any interval. The ratio of these two figures will give a measure of the efficiency of any particular set of conditions.

A typical calculation using the data of experiment number 1 will illustrate this. This reaction was allowed to proceed until it was complete, and then aliquot portions were withdrawn and the chloride ion content and total acidity determined. Thus, at the end of three days, it was found that the reaction was complete and that 5 cc. samples of the reaction mixture required 4.66 cc. of 0.1 N. silver nitrate solution and 4.30 cc. of 0.1 N. sodium hydroxide solution. A transfer of six electrons is involved in the formation of one equivalent of chloride ion according to the equation:



while two electrons are involved in the formation of one equivalent of acid, assuming the acid to be formed from the aldehyde:



Thus, on the basis of these titrations, 0.02796 (0.00466×6) equivalents of oxidizing power have been used up, and 0.00860 (0.00430×2) of them have been utilized in the formation of acid. The

TABLE 1

Experiment Number	Crotonaldehyde g.	Ba(ClO ₃) ₂ ·H ₂ O g.	OsO ₄ g.	Volume of Solution cc.	Conditions as Compared to those of Neuberg	Temperature °C.	pH of Solution at* Start of Reaction	Ratio: $\frac{\text{Acid}}{\text{Loss of Ba(ClO}_3)_2}$	Time for Completion of Reaction Days
1.	10	7.66	0.05	150	Same	25°C.	6-7	0.307	3
2.	10	7.66	0.05	150	Same	25°C.	6-7	0.237	8
3.	10	7.66	0.05	150	Same	0°C.	6-7	0.207	19
4.	10	7.66	0.05	150	Same	0°C.	6-7	0.207	19
5.	10	7.66	0.05	75	2 Conc.	0°C.	6-7	0.212	23
6.	10	7.66	0.05	300	1/2 Conc.	0°C.	6-7	0.205	14
7.	10	7.66	0.05	600	1/4 Conc.	0°C.	6-7	0.210	21
8.	10	7.66	0.05	150	Same	0°C.	6-7	0.207	19
9.	10	7.66	0.025	150	1/2 OsO ₄	0°C.	6-7	0.210	20
10.	10	7.66	0.10	150	2 OsO ₄	0°C.	6-7	0.210	19
11.	10	7.66	0.0125	150	1/4 OsO ₄	0°C.	6-7	0.208	19
12.	10	7.66		150	No OsO ₄	0°C.	6-7		..
13.	10	7.66	0.05	150	Same	0°C.	6-7	0.207	19
14.	10	7.66	0.05	150	Alkaline	0°C.	9-10		..
15.	10	7.66	0.05	150	Acid	0°C.	2-3	0.290	5
16.	10	9.1 g. AgClO ₃	0.05	300	1/2 Conc.	0°C.	6-7	0.207	14

*The solution in experiment 14 was alkaline to phenolphthalein and acid to malachite green. That in experiment 15 was acid to bromphenol blue. The solutions in all other experiments were neutral to litmus.

ratio of these figures is 0.307, which is the factor appearing in Table 1 under the heading: Ratio: $\frac{\text{Acid}}{\text{Loss of Ba(ClO}_3)_2}$.

It is seen that the temperature at which the reaction is carried out and the original acidity of the solution are the only factors that influence the formation of the acid. As long as there is some osmic acid present, neither the amount of the catalyst nor the concentration of the solution seems to affect the course of the reaction. Nor does the amount of osmic acid present seem to affect the speed of the reaction. However, as shown in experiments 4-6,

the time required for the completion of the reaction is affected by the concentration of the solution as a whole, the more dilute solution reacting in a shorter time. These last two statements are further corroborated by the figures in Table 2, obtained from analyses made twelve days after the start of the reaction.

TABLE 2

No.	Remarks	Ratio Acid	Per Cent
		Loss of $\text{Ba}(\text{ClO}_3)_2$	$\text{Ba}(\text{ClO}_3)_2$ Consumed
3.	Neuberg's concentration of Crotonaldehyde	0.207	66.0
5.	Twice Neuberg's concentration of Crotonaldehyde	0.212	40.7
6.	Half Neuberg's concentration of Crotonaldehyde	0.205	84.5
9.	Half Neuberg's amount of OsO_4 ..	0.210	58.7
10.	Twice Neuberg's amount of OsO_4 .	0.210	60.0
11.	Quarter Neuberg's amount of OsO_4	0.208	60.0

Preparation of the Methyltriose

As a result of these studies, the following directions for the preparation of the desired methyltriose were drawn up. Silver chlorate¹⁴ was used in place of the barium salt as used by Neuberg in order to avoid the presence of inorganic salts in the reaction solution at the end of the reaction. The chloride ion formed by the reduction of the chlorate ion is completely precipitated as silver chloride by this change in procedure, thus simplifying the isolation of the aldehyde. Experiment 16, Table 1, shows that the course of the reaction is not affected by this change of reagent.

A solution of 191 grams (1 mole) of silver chlorate in 3 liters of distilled water is placed in a glass-stoppered bottle of

¹⁴The silver chlorate was prepared by treatment of a suspension of silver oxide in water with an aqueous solution of chloric acid obtained by treatment of a solution of barium chlorate with an equivalent amount of sulfuric acid. Gleaming white crystals of silver chlorate melting at 132° C. were obtained upon removal of the excess silver oxide and concentration of the filtrate under reduced pressure.

8-10 liters capacity and cooled in an ice pack overnight. Two hundred and ten grams (3 moles) of freshly distilled, water-white crotonaldehyde of boiling point 102°C . at 754 mm.; a solution of one gram of osmium tetroxide¹⁵ (Merck's Osmic Acid) in 200 cc. of water; and 1100 cc. of distilled water; are also packed in ice and stored overnight in order to assure thorough chilling. The next morning, the crotonaldehyde is washed into the chlorate solution with about 600 cc. of the cooled water and the mixture is shaken until most of the crotonaldehyde is dissolved. The osmium tetroxide solution is then added, and washed in with the remaining 500 cc. of cooled water. The mixture is then vigorously shaken and again placed in the ice pack where it is stored with occasional shaking for fourteen days. At the end of this time the solution is dark in color, indicating that the reaction is complete. The odor of crotonaldehyde, which was quite strong at the beginning of the reaction, is practically gone, again indicating completion of the reaction. The color of the solution is presumably due to the presence of dark-colored lower oxides of osmium which are formed by the reduction of the tetroxide after all of the chlorate has been removed from solution. This color has been observed in many oxidation experiments in which osmium tetroxide has been used as a catalyst.¹⁶ The appearance of color in the solution indicates the disappearance of the oxidizing agent and marks the end of the reaction.

A solution of 1 gram of silver chlorate in about 15 cc. of water is now added to the reaction mixture and the bottle is well-shaken. In the course of half an hour the color disappears and the solution again becomes colorless. The clear solution is filtered to remove the precipitated silver chloride and then extracted with benzene until a sample of the solution does not cause the formation

¹⁵Care must be exercised at all times when working with this reagent in a concentrated solution because of the deleterious effect it has upon the mucous membrane of the eyes, nose and lungs. It is advisable to wear gas-tight goggles and to work in a well-ventilated hood when handling the reagent. The pure material was dissolved by breaking the thoroughly-cleaned capsule in which the oxide is purchased, in a heavy-walled, glass-stoppered bottle containing the proper amount of water. The capsule is broken by violent shaking of the bottle. Because of the strong reducing action of all organic matter on the reagent, it is necessary that the container be scrupulously clean.

¹⁶Geza Braun, J. Am. Chem. Soc., 51, 234 (1929).

of a pink color when warmed with a solution of thiocarbamide containing a few drops of hydrochloric acid.¹⁷ Failure of this test indicates the absence of osmium tetroxide. Three extractions with 300 cc. of benzene are usually sufficient. The aqueous solution is then exactly neutralized with a solution of barium hydroxide and subjected to complete distillation at reduced pressure at a bath temperature not exceeding 35° C. This procedure yields a rather viscous syrup as a residue.

This residue is shaken with about 2 liters of absolute alcohol until no more solution takes place. A white salt, the barium salt of the acid formed in the oxidation reaction separates out during the extraction. The clear supernatant liquid is decanted and the salts washed with fresh absolute alcohol to remove any occluded sugar. The washings are added to the original extract and the combined solution concentrated as before to a thick syrup, which is again taken up in one and one-half liters of absolute alcohol. The solution is allowed to stand overnight, during which time it deposits more solid matter which is removed as before. The alcoholic solution and washings are once more concentrated at reduced pressure, the concentration now being continued until the syrup is so thick that it will scarcely flow under its own weight when the flask containing it is tilted. This syrup is taken up in one liter of absolute alcohol, after which six liters of ether are added. Upon addition of the ether, the solution becomes cloudy. It is allowed to stand overnight to allow this precipitated inorganic matter to settle out. Next day, the clear solution is decanted from the small amount of solid and is again concentrated at reduced pressure, the concentration finally being carried out completely at a pressure of 2 mm. and a temperature of 35° C.

The residue now has a glassy appearance and is so viscous that the flask containing it can be inverted without the syrup moving perceptibly for a period of twenty minutes. It contains no inorganic matter, as may be shown by igniting a sample on a piece of platinum foil; the sample burns with a blue flame giving rise to a caramel-like odor, but leaves no ash.

In five successive preparations carried out according to the above directions and using the amounts of materials indicated

¹⁷Chugaev, Comptes rendu, 167, 235 (1918).

(three moles of crotonaldehyde) the following yields of syrup were obtained: 210 g.; 194 g.; 221 g.; 204 g.; and 216 g. Based on a theoretical yield of 312 g. of the methyltriose, these figures represent yields of 67.3, 62.2, 70.8, 65.4, and 69.2 per cent respectively.

The syrup possesses a light golden color and is quite transparent. It has a sweet, sickening odor and a sharp, burning taste. It is miscible in all proportions with water, the lower alcohols, acetone, and dioxane and is quite soluble in pyridine and in ether. Its slow rate of solution in the latter is deceiving; it goes into solution readily, however, when the mixture is thoroughly shaken.

Analysis: A sample of 0.003609 g. of the syrup as prepared above gave 0.006000 g. of CO_2 and 0.00257 g. of H_2O . Calculated for $\text{C}_4\text{H}_8\text{O}_3$: C, 46.15; H, 7.69. Found: C, 45.34; H, 7.77. A thin layer of the syrup was then spread out on a watch crystal and dried to constant weight over calcium chloride and paraffin in a vacuum dessicator. A sample of 0.004654 g. of this material gave 0.007835 g. of CO_2 and 0.00324 g. of H_2O . Found: C, 45.91; H, 7.79.

The reducing power of the syrup was tested by titration of an aqueous solution against Benedict's solution. It was found to have but 62 per cent of the reducing power of an equal weight of d-glucose. Thus, in a quantitative test, it was found that 0.01852 g. of the methyltriose syrup was required to reduce the same volume of Benedict's solution that was reduced by 0.01152 g. of d-glucose. This agrees with the results of Wohl and Frank who found that their syrup had but 60 per cent the reducing power of d-glucose.

Several attempts were made to crystallize the syrup, but none was successful. These attempts included the use of solvents and combinations of solvents, at ordinary and at reduced temperatures.

It was thought possible that the impurities that caused the golden color were responsible for the failure of the syrup to crystallize and so a method for the production of a colorless syrup was sought. It was found that a colorless solution could be obtained by refluxing a 50 cc. sample of a ten per cent aqueous solution of the syrup for 45 minutes with one gram of animal charcoal (Nuchar, grade XXX was found to be quite satisfactory). The colorless solution was colored again, however, after two hours standing, even in an atmosphere of nitrogen gas. The reducing power of the treated solution remained the same during the treatment. Another sample of

the syrup was refluxed with charcoal, filtered, and concentrated at reduced pressure and a temperature of 25°C . as soon as it became colorless, but here again the solution darkened during concentration with the results that a syrup, similar in color to the original sample, was obtained. Thus, it is apparent that the color of the original syrup is due to an impurity, since it may be removed without impairing the reducing power of the syrup. However, the pure, colorless syrup produces this impurity again and does not remain colorless in any appreciable concentration for longer than a few hours. The figures obtained in the elementary analyses of the substance, reported above, show that the amount of impurity present must be very small.

Simultaneously with these tests, several attempts were made to distill the syrup at reduced pressures. At pressures of about 2 mm., approximately 25 per cent of the material distilled over a range from $145\text{--}165^{\circ}\text{C}$. as a yellow, viscous liquid that resembled the original syrup in appearance. It flowed so slowly as almost to clog the delivery tube of the distilling flask. It had a much sharper odor than the original syrup, and possessed only 68 per cent of the reducing power of that material. The residue in the flask had charred considerably and possessed practically no reducing power. Only in those cases in which high vacuum was employed did distillation offer any signs of success. At a pressure of 5×10^{-2} mm. and a bath temperature of 90°C ., a colorless distillate was obtained. It possessed the sharp, penetrating odor of the original syrup and, like it, was miscible with water. It reduced Benedict's solution strongly and was shown, by quantitative test, to have the same reducing power as the original syrup.

Analysis: A sample of 0.2043 g. of substance gave 0.03450 g. of CO_2 and 0.1443 g. of H_2O . Calculated for $\text{C}_4\text{H}_8\text{O}_3$: C, 46.15; H, 7.69. Found: C, 46.06; H, 7.90.

Distillation was of little value as a method of purification of the syrup, however, because this product, too, took on the color of the original syrup in less than an hour after the distillation. Furthermore, the yield was quite low, due to extensive decomposition of the material in the distilling flask during the distillation.

Derivatives of the Methyltriose

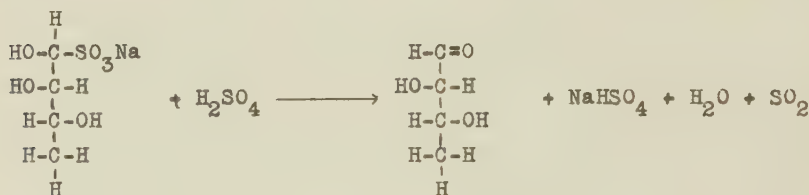
Further confirmation of the identity of the syrup was

obtained by the preparation and analysis of two derivatives: the sodium bisulphite addition product and the phenylosazone.

The Sodium Bisulfite Addition Product.--To a sample of the syrup was added an equal weight of sodium bisulfite in saturated water solution. The mixture was shaken and warmed on the steam bath (5 minutes) until a clear solution was obtained. It was then allowed to stand overnight. During this time, the solution set to a solid mass of white crystals. These were collected on a filter and recrystallized twice from 75 per cent alcohol. The yield of the crude material was quantitative; that of the purified material was about 90 per cent of the theoretical.

Analysis: A sample of the compound was analyzed for sulfur by oxidation with nitric acid and precipitation of the sulfate ion as barium sulfate. A sample of 0.2226 g. of substance gave 0.2460 g. of BaSO_4 . Calculated for $\text{C}_4\text{H}_9\text{SO}_6\text{Na}$: S, 15.33. Found: S, 15.15.

The recovery of the aldehyde from the addition compound was best brought about in the following manner. An exactly equivalent amount of sulfuric acid, based on the equation:



was added to a dilute aqueous solution of the addition compound and the solution allowed to stand for five days, at the end of which period the reducing power of the solution had reached a maximum. The inorganic salts were then removed by precipitation with alcohol, followed by the concentration of the filtrate to a syrup, extraction of this with absolute alcohol and then subsequent concentration of this solution at reduced pressure. A syrup similar in color to the original syrup and possessing practically the same reducing power was obtained.

Unless the aldehyde is to be kept for a very long period of time, or unless a solid derivative that may be hydrolyzed to yield the aldehyde in solution is particularly desired, it is of no value to prepare the addition compound, since it is not possible, by its preparation and subsequent hydrolysis, to obtain a purer syrup than that obtained directly by the oxidation of the croton-

aldehyde. Furthermore, the syrup, once obtained, and except for the production of a slight color, seems to be quite stable if it is kept in a tightly stoppered container or in a vacuum dessicator. Samples of it have been kept in the laboratory under these conditions for periods of several months without any evidence of decomposition or loss of reducing power.

The Phenyllosazone.--When the syrup was treated with phenylhydrazine according to the directions of Wohl and Frank, golden needles of the phenyllosazone were obtained. The directions of Wohl and Frank are given below.

A sample of the syrup is dissolved in 3 volumes of water and the solution treated with 3 molecular quantities of freshly-distilled phenylhydrazine dissolved in an equal volume of acetic acid. The reaction mixture is kept in a closed flask at 37° C. for three days, at the end of which time yellow crystals and a brown oil have appeared. The former are separated by suction filtration and recrystallized from benzene. The purified crystals are obtained in 20 per cent yield and melt at 171.5°C. (corr.).

The osazone was prepared according to the directions above, with the exception that the reaction flask was warmed for 15 minutes on the steam bath after mixing the reagents, and then was allowed to stand at room temperature for 3 days to allow the crystals to form. Three grams of the syrup gave 2.0 grams of the crude crystals, which were recrystallized from benzene and then melted at 173.5°C., which compares favorably with the melting points obtained by Wohl and Frank (171.5°), Dills and Stephan (171.5°) and Glattfeld and Straitiff (173°). One and seven-tenths grams of the pure material were obtained, representing a yield of 21 per cent.

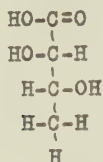
Analysis: Samples of 0.2760 g. and 0.2150 g. of the crystals gave 49.90 cc. of N₂ at 25°C. and 754.4 mm. and 39.20 cc. of N₂ at 28° C. and 751.3 mm., respectively. Calculated for C₁₆H₁₈N₄O: N, 19.86. Found: N, 20.07 and 19.98.

Proof of Configuration of the Methyltriose

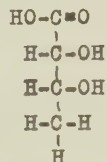
The configuration of the sugar was determined by oxidation to the corresponding α,β-dihydroxy-butyric acid. The two dl forms of this acid have been prepared by Glattfeld and Woodruff¹⁸ and shown to have melting points of 74° and 81.5° C. Braun showed

¹⁸Glattfeld, and Woodruff, J. Am. Chem. Soc., 49, 2309 (1927).

the acid of melting point 74° to be the threo-acid and that of melting point 81.5° to be the erythro-acid.¹⁹

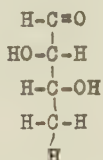


threo α,β Dihydroxy-
butyric Acid
m.p. 74° C.



erythro α,β Dihydroxy-
butyric Acid
m.p. 81.5° C.

The α,β dihydroxy-butyrlic acid obtained by oxidation of a sample of the methyltriose was the threo-acid of melting point 74° C. The methyltriose therefore has the configuration:



The first oxidizing agents tried were found to be unsatisfactory. Both potassium permanganate and silver oxide lead to the complete breakdown of the molecule, with the result that no solid acids could be found in the reaction mixture. Thirty per cent hydrogen peroxide gave similar results, while the three per cent hydrogen peroxide produced oxalic acid. Bromine was found to give the desired result.

Oxidation of the Syrup with Bromine.--Ten grams of the syrup was dissolved in 50 cc. of water, the solution treated with 16 grams of bromine and the mixture allowed to stand in the dark in a glass-stoppered Erlenmeyer flask. The mixture was occasionally shaken. The layer of liquid bromine disappeared in the course of one hour and the entire solution was colorless within six hours. The mixture was then concentrated to dryness at reduced pressure. However, as the solution became more concentrated, it became dark and showed evidences of decomposition. Because strong mineral acids (such as hydrochloric and hydrobromic acids) have been found to have such an effect upon the syrup of the methyltriose, it was decided to remove the hydrobromic acid at the time of its formation

¹Geza Braun, J. Am. Chem. Soc., 52, 3179 (1930).

by means of silver carbonate. Therefore, a second experiment was carried out exactly like the first one with the same amounts of material excepting that 45 grams of silver carbonate was also introduced into the reaction mixture. Due to the evolution of carbon dioxide, formed as the reaction proceeded, the flask could not be stoppered tightly. Very little bromine escaped into the air, however, because of the speed of the reaction. All of the liquid bromine disappeared within 20 minutes and the solution was colorless within an hour. This is in agreement with the work of Hudson and Isbell²⁰ who found that bromine oxidized the aldo-hexoses to the corresponding hexonic acids quite readily in the presence of carbonates.

Separation of the Silver Salt of the Acid.--At the end of the reaction, the precipitated silver bromide and excess silver carbonate were removed by filtration and the clear filtrate was concentrated to a thin syrup at reduced pressure. Alcohol was added and a rather gummy solid was thrown down. The liquid was decanted and the residue again treated with alcohol and triturated until it became crystalline. This solid weighed 8.5 grams. It was then recrystallized twice from the least amount of hot water and finally gave 6.0 grams of beautiful gleaming white crystals. These figures represent yields of 44 and 31 per cent of silver salt respectively, calculated from the amount of syrup used.

Analysis: Samples of the pure salt were analyzed by ignition to metallic silver. Samples of 0.4418 g. and 0.2155 g. gave 0.2099 g. and 0.1023 g. respectively. Calculated for $C_4H_7O_4Ag$: Ag, 47.53. Found Ag, 47.51 and 47.47.

Separation of the Lead Salt of the Acid.--It was later discovered that litharge (PbO) could be used in place of the silver carbonate to maintain a neutral solution without affecting the course or the speed of the reaction. This material has the advantage of being more readily available as well as being cheaper than the silver carbonate. As it does not cause the evolution of gas, the reaction flask may be tightly stoppered. Five grams of the syrup were dissolved in 25 cc. of water and the solution placed in a glass-stoppered Erlenmeyer flask containing 20 grams of litharge. Seven and seven-tenths grams of bromine were added and the flask

²⁰Hudson, and Isbell, Bur. Stand. J. Res., 8, 327 (1932).

was well shaken and placed in the dark. At the end of 45 minutes the solution was colorless and a heavy precipitate of lead bromide was at the bottom of the flask. It was separated by filtration together with the excess lead oxide. Ten cc. of alcohol were then added to the filtrate and a small amount of solid matter, which was shown to contain bromide ion and was undoubtedly lead bromide, was thrown down and removed. The filtrate was then concentrated and the residue was triturated with absolute alcohol till it became crystalline. Five and one-half grams of the crystalline material was obtained.

Acid from the Silver Salt.--Four grams of the silver salt was dissolved in 15 cc. of water and the solution treated with dilute hydrochloric acid until no more silver chloride precipitated. The silver chloride was then separated and the clear solution concentrated to a thick syrup at reduced pressure at a temperature of 35° C.

Analysis: Samples of 0.2145 g. and 0.2533 g. of the syrup required 18.03 cc. and 21.31 cc. of 0.1 N. NaOH for neutralization, respectively. Calculated for $C_4H_8O_4$: neutralization equivalent, 120. Found: 119 and 119.

The Phenylhydrazine Salt of the Acid.--The phenylhydrazine salt²¹ was prepared according to the directions of Glattfeld and Woodruff.²² The syrup obtained by treating the silver salt with hydrochloric acid was dissolved in 15 cc. of 95 per cent alcohol and 5 cc. of this solution was treated with 2 cc. of freshly distilled phenylhydrazine, and the solution allowed to stand open to the air. After standing for a day, the solution was warmed on the steam bath to hasten the evaporation of the alcohol, and a white solid appeared. This was washed with ether to remove any occluded phenylhydrazine and white crystals were obtained. They were recrystallized three times from absolute alcohol and melted at 129°C. indicating that they were the phenylhydrazine salt of the three form of the α , β -dihydroxy-butyric acid. That this was really the case was shown by obtaining the melting points of mixtures with the

²¹Glattfeld, and Woodruff, loc. cit., reported this compound as the phenylhydrazide with one molecule of water of crystallization. However, Primack (Unpublished Master's thesis, Department of Chemistry, University of Chicago, 1934), and later Glattfeld, and Straitiff, loc. cit., showed it to be the phenylhydrazine salt of the acid.

²²Glattfeld, and Woodruff, loc. cit.

phenylhydrazine salts made from authentic samples of the two epimeric acids. The melting point of a one to one mixture of the crystals with those from known threo acid (m.p. 129°) was 129° C.; while that of a one to one mixture of the crystals with those from known erythro acid (m.p. 103°) was 99° to 112° C.

The Crystalline Acid.--By the time this work had been completed, a sample of the syrup which had been seeded with the crystals of the pure threo acid had become crystalline. The crystals were separated, and recrystallized from one part of hot ethyl acetate. After two recrystallizations, they melted at 73° C. The melting point did not change when the crystals were mixed with those of the known threo acid of melting point 73.5° C.

The oxidation of the Methyltriose with Mercuric Oxide.--In later attempts to improve the yield of the acid, mercuric oxide (yellow) was used as the oxidizing agent, according to the method used by Blanchieter²³ for the preparation of gluconic acid from d-glucose. Ten grams of the syrup was dissolved in 100 cc. of water and 50 grams of mercuric oxide (yellow) and 15 grams of calcium carbonate was added. The mixture was refluxed on a steam bath for fifteen hours, at the end of which time the reducing power of the solution had become practically zero. The precipitated salts (mercurous oxide and excess calcium carbonate) were separated and the filtrate was saturated with hydrogen sulfide to remove any dissolved mercury salts. The filtrate from the mercury sulfide was then concentrated at reduced pressure and the residue treated with alcohol and triturated until the solid mass that was thrown down became crystalline. It was recrystallized from 50 per cent alcohol. Four and seven-tenths grams of the calcium salt were obtained by this treatment, representing a yield of 33 per cent, based on the amount of methyltriose used.

Analysis: Weighed samples of the calcium salt were dissolved in water, the calcium precipitated as the oxalate and collected on an asbestos mat in a Gooch crucible. The oxalate content of the precipitate was then determined volumetrically with standard permanganate. Samples of 0.1318 g. and 0.1254 g. of substance required 8.90 cc. and 8.45 cc. of 0.1 N. KMnO_4 respectively. Calculated for $(\text{C}_4\text{H}_7\text{O}_3)_2\text{Ca}\cdot\text{H}_2\text{O}$: Ca, 13.52. Found: Ca, 13.48 and 13.55.

Acid from the Calcium Salt.--The calcium salt was decom-

²³Blanchieter, Bull. soc. chim. (4) 33, 346 (1923).

posed in the usual manner by means of sulfuric acid, 3.7 grams of the concentrated acid being added to a solution of 10 grams of the calcium salt dissolved in 10 cc. of water. The mixture was concentrated to a thin syrup and was then treated with 30 cc. of absolute alcohol to remove the inorganic matter. The filtrate was reconcentrated and the syrup obtained was added to that obtained from the silver salt and allowed to crystallize.

The Preparation of dl-threo- β -Diacetoxy-butylaldehyde.--

Further evidence for the threo configuration of the methyltriose was obtained by preparing the diacetoxy derivative and showing that it was different from the diacetoxy derivative of the erythro form of this dl-d, β -dihydroxy-butylaldehyde prepared by Glattfeld and Straitiff²⁴ and from the dl-d, β -diacetoxy-isobutylaldehyde prepared by Glattfeld and Mochel.²⁵

Ten grams (0.1 mole) of the methyltriose syrup was placed in a flask fitted with a reflux condenser protected from moisture by means of a calcium chloride tube, and carefully treated with 47 grams (0.6 mole) of acetyl chloride (Merck's reagent). The reaction flask and contents were cooled from time to time to prevent too violent a reaction. Large amounts of hydrogen chloride were evolved and the solution became dark in color. This darkening in color was noticed whenever the sugar was in contact with strong mineral acids and was probably due to these. When the vigorous reaction had subsided, the flask was warmed on the steam bath until the evolution of the gas ceased (usually 6 hours). The solution was then placed in a Claisen flask and concentrated at 30 mm. and 50° C. When no more liquid distilled at this pressure, the pressure was reduced to 3 mm. The distillate was collected in three fractions. Fraction 1, from 45-65°, weighed 3 grams and was a very light-yellow liquid. It was acidic, miscible with water, and was shown by test to contain large amounts of chloride ion. It did not reduce Benedict's solution. It was probably a mixture of hydrogen chloride, acetyl chloride and acetic acid. Fraction 2, from 80-100°, weighed 8 grams (42 per cent of the theory based on the amount of syrup used) and was a light-yellow liquid. It was acid to litmus and reacted with water with the production of heat. It reduced

²⁴Glattfeld, and Straitiff, loc. cit.

²⁵Glattfeld, and Mochel, loc. cit.

Benedict's solution strongly and gave but a faint test for chloride ion. Fraction 3 distilled at temperatures above 135°C. , weighed 3 grams, and was a yellow, viscous liquid. This fraction distilled in much the same manner as the aldehyde syrup when the latter was distilled at this pressure. It showed the same tendency to clog the condenser and the delivery tube of the distilling flask. It possessed but one-half the reducing power of the original syrup. There were also 2 grams of charred residue, which possessed no reducing power.

TABLE 3
THE DISTILLATION OF ACETYLATED PRODUCT
FROM TEN GRAMS OF SYRUP

Fraction	Weight g.	Boiling Range $^{\circ}\text{C.}$
1	3	45-65
2	8	80-100
3	3	Above 135
Residue	2	

The experiment was repeated with the same amount of material and this time yielded 7 grams of the fraction of boiling range $80-100^{\circ}$. This was added to the fraction of this boiling range from the first experiment, and the 15 grams of material fractionated at 4 mm. pressure. In this distillation 12.5 grams of material of boiling range $93-99^{\circ}$ was obtained, which, upon refractionation, yielded 10.2 grams of material of boiling range $95-97^{\circ}\text{C.}$ at 4 mm. These amounts correspond to yields of diacetoxy-aldehyde of 35 and 28.6 per cent, respectively, based on the aldehyde syrup used. The material was light yellow in color and had a rather sharp odor.

Analysis: The fraction of boiling range $95-97^{\circ}\text{C.}$ was analyzed by titration and for carbon and hydrogen with the following results.

Samples of 0.5951 g. and 0.8972 g. required 63.92 cc. and 95.60 cc. of 0.1 N. NaOH respectively. Calculated for $\text{C}_8\text{H}_{12}\text{O}_5$: neutralization equivalent, 94. Found: 93.5 and 93.9.

Samples of 0.003630 g. and 0.003567 g. of substance gave 0.00209 g. and 0.00208 g. of H_2O and 0.006805 g. and 0.006680 g. of CO_2 , respectively. Calculated for $\text{C}_8\text{H}_{12}\text{O}_5$: C, 51.06; H, 6.38.

Found: C, 51.13 and 51.07; H, 6.44 and 6.52.

Glattfeld and Straitiff reported that the diacetyl derivative of the dl-erythro α,β -dihydroxy-butyraldehyde distilled at 87° at 4 mm. and Glattfeld and Mochel reported that the diacetyl derivative of dl- α,β -dihydroxy-isobutyraldehyde boiled at 104° at 30 mm. Obviously, the diacetyl derivative of the methyltriose under discussion is not identical with either of these.

Several other procedures were used in attempts to increase the yield of the diacetyl-methyltriose. Thus, the syrup was treated with greater excesses of acetyl chloride than that mentioned above, and the treatment was continued over longer periods of time. Acetic anhydride which contained various amounts of hydrogen chloride was also used and the reaction was carried out in the presence of pyridine and of dioxane, the latter being used as a diluent, in an attempt to lower the amount of decomposition of the methyltriose. These experiments led to the following conclusions.

(a) Some catalyst, such as hydrogen chloride, must be present. This catalyst may be added either to acetic anhydride as the dry gas, in which case it must be present to the extent of from three to five per cent of the weight of the reagent, or it may be furnished by the acetyl chloride if that reagent is used.

(b) At least three times the theoretical amount of acetylating reagent should be present.

(c) The yield is not improved by refluxing the solution after the evolution of hydrogen chloride has ceased when acetyl chloride is used, or by refluxing for more than six hours when acetic anhydride is used.

(d) Decomposition, as evidenced by the darkening of the solution, is not reduced by the use of a diluent such as dioxane, nor is the yield of the product improved by such a procedure.

Attempt to prepare the Diethylacetal of dl-threo α,β -Dihydroxy-butyraldehyde.--At this stage of the work, it was decided to attempt the preparation of the diethylacetal of the methyltriose so that its properties might be compared with those of the acetal prepared by Wohl and Frank.²⁶ Such a comparison would definitely prove the configuration of the methyltriose reported by them, and the compound might also prove useful in attempts to bring about the

²⁶Wohl, and Frank, op. cit.

crystallization of the methyltriose syrup. Witzemann²⁷ reported that glyceraldehyde could be best obtained in the crystalline form by the careful hydrolysis of its diethylacetal.

Four experiments were carried out to determine the best method for preparing the acetal. The characteristics of each are indicated in Table 4. The solutions were allowed to stand at room temperature in tightly stoppered flasks for two weeks, at the end of which time the color and reducing power of each were noted. All

TABLE 4

Number	Methyltriose g.	Absolute Alcohol g.	Catalyst		
			HCl g.	$\text{HC}(\text{OC}_2\text{H}_5)_3$ g.	NH_4Cl g.
1.	5	40	1.2		
2.	5	40	1.2	20	
3.	5	40	...	20	
4.	5	40	...	20	0.25

of the solutions had darkened somewhat. Those that contained hydrogen chloride were black, while the solution in experiment 3 was the lightest in color. Titrations against Benedict's solution showed that the solution in experiment 2 had practically no reducing power, that in experiment 4 possessed some, that in experiment 1 a little more, while that in experiment 3 possessed the most.

The reaction mixtures were then fractionated at 12 mm. The material that came over below 60° was mostly alcohol, orthoformic ester and ethyl formate. This fraction was discarded in all cases. The greater part of the residue, after the removal of this low boiling fraction, distilled from 95-130° C. The four experiments gave the following amounts of this fraction: (1) 2.5 g.; (2) 6.1 g.; (3) 2.9 g.; (4) 4.0 g., representing, respectively, yields of 29.2, 71.5, 34, and 47 per cent of the theoretical yield of the diethylacetal. The material remaining in the flask after the removal of this fraction distilled above 160° C. in a manner that resembled that of the methyltriose; it was discarded. The 95-130° fractions were combined and refractionated at 12 mm. pressure; 10.6

²⁷Witzemann, J. Am. Chem. Soc., 36, 1913 (1914).

grams of material was collected from 103-122° C. The refractionation was repeated until 5.6 grams of a colorless, rather viscous liquid was obtained that could be repeatedly distilled at 116-117.5° C. at 12 mm. or at 71° C. at 2mm. Wohl and Frank reported that the diethylacetal prepared by them was a colorless, slightly mobile liquid that distilled at 114-116° C. at 12 mm. and gave a proper analysis for carbon and hydrogen.

Analysis: The material collected at 116-117.5° C. at 12 mm. was analyzed for carbon, hydrogen and ethoxy content. Samples of 0.002764 g. and 0.002831 g. gave 0.005826 g. and 0.005984 g. of CO₂ and 0.002322 g. and 0.002357 g. of H₂O. Calculated for C₈H₁₈O₄; C, 53.93; H, 10.11. Found: C, 57.49 and 57.65; H, 9.40 and 9.31.

A sample of 0.003517 g. gave 0.008203 g. of AgI. Calculated for C₈H₁₈O₄; OC₂H₅, 50.56. Found: OC₂H₅, 44.70.

Evidently, although the material obtained came over at a constant temperature when distilled at two different pressures, a mixture was obtained. The distillate undoubtedly contained some of the diethylacetal of the methyltriose in conjunction with some other substance, possibly a decomposition product. As noted, the material that was analyzed distilled over practically the same range as did the compound prepared by Wohl and Frank. However, due to lack of time, the material was not examined further.

CONCLUDING REMARKS

The program for the study of the saccharinic acid rearrangement of the tetroses has reached the point where it is desirable to have available certain dihydroxy-butyraldehydes. These are substances that should yield a much smaller number of products under rearrangement conditions than the tetroses which it is proposed ultimately to study. These aldehydes, therefore, should yield information of the greatest value for an attack on this problem. Two of the aldehydes have already been prepared in these laboratories and this dissertation reports the preparation and properties of a third.

The methyltriose, dl-threoα,β-dihydroxy-butyraldehyde has been prepared from crotonaldehyde by an adaptation of the method of I. S. Neuberg for the preparation of dl-glyceraldehyde from acrolein. In the new procedure, the crotonaldehyde is oxidized to

methyltriose in one step and the method is therefore a decided improvement upon that of Wohl and Frank, which involves the preparation and isolation of three intermediates in passing from the crotonaldehyde to the methyltriose. The yield in the new method is about 67 per cent as compared with Wohl's yield of 15.7 per cent.

In the course of the work, the sodium bisulfite addition product and the osazone have been prepared.

The methyltriose has been oxidized to the corresponding C₄-saccharinic acid, dl-threo α , β -dihydroxy-butyric acid, of known configuration, which proves the configuration of the methyltriose to be that of the threo or trans form.

The methyltriose has been converted into a diacetyl-compound which is different from the diacetyl-compound of the epimeric erthro-methyltriose, a fact which corroborates the configuration assigned to it.

The preparation of the diethylacetal of the methyltriose has been attempted, but the compound isolated was not pure.

